The effects of Ramadan fasting on patients with prosthetic heart valve taking warfarin for anticoagulation

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Introduction: Oral anticoagulation with warfarin is indicated for patients with prosthetic heart valves. The effects of religious fasting during Ramadan month (in the Islamic calendar) on anticoagulation aren't clear.

Objectives: To study the impact of Ramadan fasting on international normalized ratio (INR), quality of anticoagulation, dose of warfarin used and blood osmolarity.

Methods: 18 patients were followed-up prospectively for 3 months (pre- Ramadan, Ramadan and post-Ramadan months). Patients presented for weekly visits in which blood samples were obtained.

Results: No significant difference in INR and warfarin dose was found between Ramadan month, and months before and after it. The post-Ramadan INR was significantly larger than pre-Ramadan (p = 0.004). Blood osmolarity was significantly lower during Ramadan compared to pre- and post-Ramadan months. A significantly better quality of anticoagulation was noticed during Ramadan (p < 0.001). A significantly larger ratio of supratherapeutic INR values occurred in the post-Ramadan month (p < 0.05). A significantly larger ratio of infra-therapeutic INR values was noticed in the pre-Ramadan month (p < 0.05).

Conclusion: No significant difference in mean INR or warfarin dose was found and a better quality of anticoagulation was achieved during Ramadan. A tendency toward supra-therapeutic anticoagulation occurred after Ramadan, thus a closer follow up during this period may be reasonable.

Introduction

Patients with prosthetic heart valves (PHVs) require chronic oral anticoagulation. Although newer oral antithrombotic agents (rivaroxaban, apixaban, dabigatran, etc.) are now available, current guidelines do not recommend their use for antithrombotic therapy in patients with PHVs [1–3]. Vitamin K antagonists (mainly warfarin) remain the most widely used agents for this purpose.

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During the 9th month of the Islamic calendar, the month of Ramadan, Muslims fast from sunrise to sunset. Since it is emphasized that patients' diet may affect the efficacy of anticoagulation, clinicians are frequently faced with the question whether a patient taking warfarin can fast or not.

Materials and methods

The study was conducted between May 22, 2015 and August 14, 2015. The study was approved by the Ethics Committee of the Dr Siyami Ersek Cardiovascular and Thoracic Surgery Educational and Research Hospital, Istanbul, Turkey.

The hospital records were screened for adult patients living in Istanbul and taking warfarin who underwent mitral, aortic, or tricuspid valve replacement surgery between April 2014 and March 2015. 243 patients were contacted by phone and given brief information about the study. The patients were invited for an initial assessment visit in which they were provided with further details of the study, their demographic information was recorded and they underwent a medical assessment to ensure they were fit to fast.

A schedule of 12 weekly follow-up visits was prepared. Four visits were in the pre-Ramadan month, four during Ramadan, and four in the post-Ramadan month. In each visit, blood samples were obtained to measure international normalized ratio (INR) and the total amount of warfarin used in the previous week was recorded. Biochemical markers for hepatic dysfunction (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transferase, total protein, and albumin) were also obtained. Sodium, potassium, blood urea nitrogen (BUN), and glucose levels were obtained and used to calculate blood osmolarity using the equation:

$$2 \times (Na + K) + (Glucose/18) + (BUN/2.8). \quad (1)$$

Signs and symptoms of major bleeding and thrombotic events were questioned in each visit.

The therapeutic INR range used in our study was 2.0–3.50. The warfarin dose was adjusted when the INR values were out of this range. Patients were asked to take warfarin when they woke up for the meal of suhur (the meal just before sunrise). No adjustment of the other medications was made and no specific instructions about when to take them was made. Patients continued to take diuretics during Ramadan in their usual doses. Enoxaparin was prescribed for 5 days when subtherapeutic INR values were obtained.

The primary outcome of this study is the mean INR value before, during, and after Ramadan.

Abbreviations

PHV   prosthetic heart valve
INR   international normalized ratio
AST   aspartate aminotransferase
ALT   alanine aminotransferase
GGT   gamma-glutamyl transferase
ALP   alkaline phosphatase
BUN   blood urea nitrogen
AVR   aortic valve replacement
MVR   mitral valve replacement
BMI   body mass index

Secondary outcomes are the dose of warfarin used, quality of anticoagulation, blood osmolarity, and any biochemical evidence of hepatic dysfunction that may cause variation in the INR before, during, and after Ramadan. Clinical endpoints for termination of the study included any major hemorrhagic or thrombotic events.

Descriptive statistics were used to report patients' demographic data. Data are expressed as mean ± standard deviation for continuous variables and percentages for categorical variables. Paired sample t test was used to compare the variables in the three study periods (pre-Ramadan, Ramadan, and post-Ramadan). A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM-SPSS Inc., Armonk, NY, USA).

Results

Thirty-six patients presented for the initial visit. Two patients were considered medically unfit to fast and they were excluded from the study (these patients were both frail, elderly, diabetic, and on multiple medications). Nine patients did not consent to the study protocol. Three patients could not tolerate fasting this year so they were excluded on the first follow-up visit in Ramadan. Four patients were lost to follow up (these 4 patients went to their hometowns to celebrate the feast after Ramadan and they then spent the summer vacation there). Eighteen patients met the minimum criteria for inclusion in the study, which were as follows: patients who presented for follow up at least twice before and during Ramadan and at least once after Ramadan. Details of our patient recruitment process are illustrated in Fig. 1.

The study cohort included 12 (66.7%) men and six women. The mean age was 52.7 ± 13.2 years. Twelve participants had mitral valve replacement and six participants had aortic valve replacement;
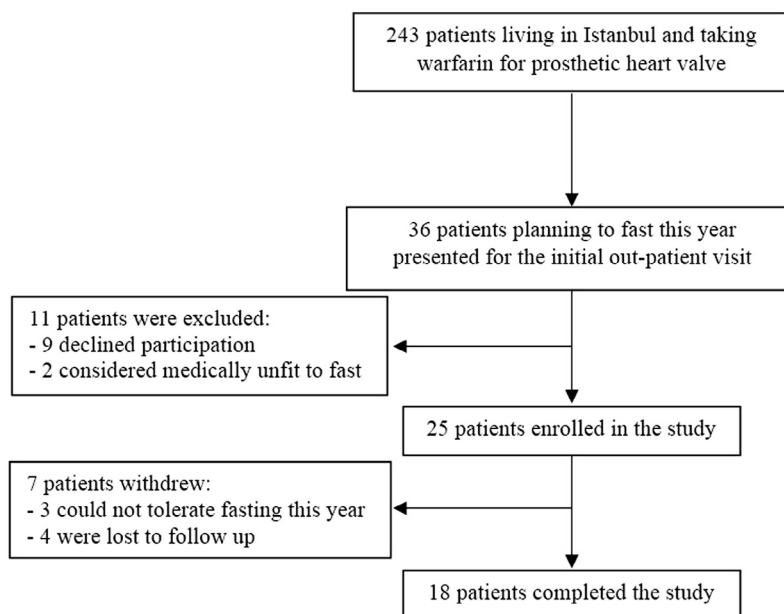
Figure 1. Consort study algorithm.

there were no cases of both valves being replaced. Five patients had normal body mass index, eight patients were overweight, and five patients were obese. The mean body mass index was 28.47 ± 4.89 kg/m^2. No major hemorrhagic or thrombotic event was recorded. The demographic data of the study population are summarized in Table 1.

The mean values of the blood tests were calculated for the three study periods as shown in Table 2. The mean INR in the post-Ramadan month was insignificantly higher compared to Ramadan ($p = 0.059$). The mean INR was significantly higher in post-Ramadan compared to pre-Ramadan (2.47 ± 0.57 vs. 3.05 ± 0.69, respectively; $p = 0.004$). No statistical difference in the mean warfarin dose taken was found. Biochemical markers of hepatic dysfunction did not show a significant difference between the three study periods. Surprisingly, the mean osmolarity was significantly lower during Ramadan compared to the pre- and post-Ramadan periods ($p = 0.048$ and $p = 0.038$, respectively).

Fluctuation in the quality of anticoagulation throughout the study is illustrated in Fig. 2 and Table 3. The highest ratios of therapeutic anticoagulation were recorded in the last 2 weeks of Ramadan (88.89% and 87.5%). The lowest ratio of therapeutic anticoagulation was noticed in the 1st week after Ramadan (60.0%). Seventy percent of INR values obtained in the pre-Ramadan month were within the therapeutic range, 82.1% in Ramadan, 75.5% in the post-Ramadan month and the overall ratio throughout the 3-month study period was 76.1%. No significant difference was found between the pre- and post-Ramadan months ($p = 0.159$). However, a significantly higher ratio of therapeutic INR was found during Ramadan compared to the pre- and post-Ramadan months (both $p < 0.001$). Of the INR values obtained during the post-Ramadan period, 18.9% were supratherapeutic, compared to 6.7% in the pre-Ramadan and 4.5% in the Ramadan period

Table 1. Patient demographics.

	Study population ($n = 18$)
Median age, y	52.7 ± 13.2
Age groups (y)	
$\leqslant 45$	5 (27.8)
45–60	9 (50.0)
$\geqslant 60$	4 (22.2)
Sex	
Male	12 (66.7)
Female	6 (33.3)
Surgery	
MVR	12 (66.7)
AVR	6 (33.3)
Mean BMI, kg/m^2	28.47 ± 4.89
BMI groups	
20–25 kg/m^2 (Normal)	5 (27.8)
25–30 kg/m^2 (Overweight)	8 (44.4)
$\geqslant 30$ kg/m^2 (Obese)	5 (27.8)

Data are presented as n (%) or mean ± standard deviation.
AVR = aortic valve replacement; BMI = body mass index; MVR = mitral valve replacement.

Table 2. Results of blood tests expressed as the mean values of the tests in each of the study periods (mean ± standard deviation).

	Pre-Ramadan	Ramadan	Post-Ramadan	p		
				Pre-Ramadan vs. Ramadan	Ramadan vs. post-Ramadan	Pre-Ramadan vs. post-Ramadan
Mean INR	2.47 ± 0.57	2.67 ± 0.37	3.05 ± 0.69	0.183	0.059	0.004[*]
Mean weekly warfarin dose (mg)	36.68 ± 12.25	37.78 ± 12.81	36.56 ± 14.11	0.516	0.305	0.959
Mean calculated osmolarity (mosm/kg)	299.5 ± 3.94	297.9 ± 3.98	298.6 ± 3.85	0.048[*]	0.460	0.038[*]
Mean ALP (U/L)	88.57 ± 23.51	89.31 ± 32.49	86.69 ± 18.86	0.844	0.376	0.156
Mean potassium (mEq/L)	4.42 ± 0.42	4.53 ± 0.40	4.37 ± 0.44	0.103	0.033[*]	0.530
Mean sodium (mEq/L)	139.67 ± 1.40	138.59 ± 1.80	139.47 ± 1.21	0.010[*]	0.198	0.092
Mean albumin (g/dL)	4.35 ± 0.25	4.43 ± 0.29	4.30 ± 0.29	0.009[*]	0.027[*]	0.610
Mean total protein (g/dL)	7.68 ± 0.34	7.76 ± 0.41	7.59 ± 0.46	0.069	0.050	0.344
Mean GGT (U/L)	33.28 ± 23.55	31.85 ± 23.46	30.65 ± 22.09	0.409	0.055	0.518
Mean AST (U/L)	21.84 ± 4.26	21.67 ± 4.22	23.11 ± 6.64	0.816	0.275	0.122
Mean ALT (U/L)	18.09 ± 5.99	18.56 ± 8.54	18.39 ± 8.49	0.792	0.210	0.819
Mean BUN (mg/dL)	16.22 ± 3.47	17.46 ± 4.79	15.54 ± 3.17	0.219	0.104	0.281
Mean glucose (mg/dL)	101.34 ± 23.64	101.19 ± 18.10	97.77 ± 26.62	0.963	0.127	0.153

Data are presented as mean ± standard deviation.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; GGT = γ-glutamyl transferase; INR = international normalized ratio.
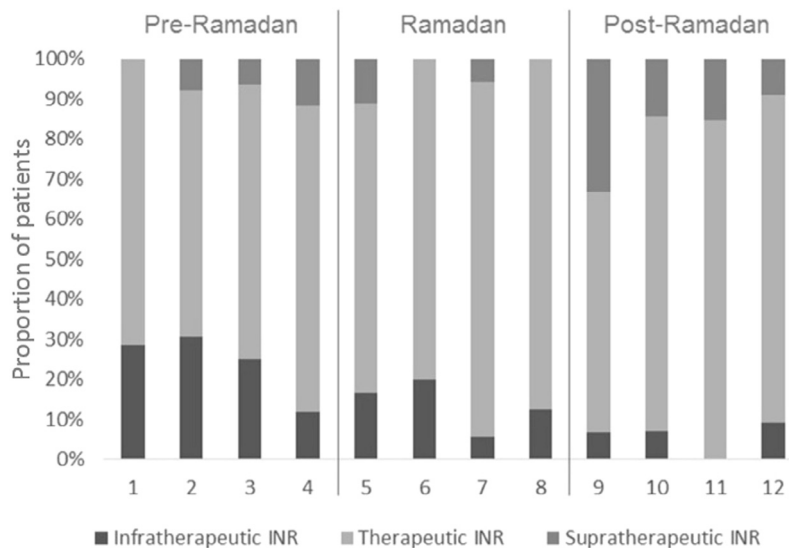[*] $p < 0.05$.

Figure 2. Fluctuation in quality of anticoagulation throughout the study weeks.

Table 3. Percentage of international normalized ratio (INR) values according to the therapeutic range across the study periods.

	Pre-Ramadan	Ramadan	Post-Ramadan	p		
				Pre-Ramadan vs. Ramadan	Ramadan vs. post-Ramadan	Pre-Ramadan vs. post-Ramadan
Supra-therapeutic INR	6.7 (4)	4.5 (3)	18.9 (10)	0.709	0.001[*]	0.013[*]
Therapeutic INR	70 (42)	82.1 (55)	75.5 (40)	<0.001[*]	<0.001[*]	0.159
Infra-therapeutic INR	23.3 (14)	13.4 (9)	5.7 (3)	<0.001[*]	0.083	0.044[*]

Data are presented as % (*n*).
[*] $p < 0.05$.

($p = 0.013$ and $p = 0.001$, respectively). Of the INR values obtained during the pre-Ramadan period, 23.3% were infratherapeutic, compared to 5.7% post-Ramadan and 13.4% in the Ramadan period ($p = 0.044$ and $p < 0.001$; respectively). The largest difference in anticoagulation quality between 2 consecutive weeks was noticed between the last week of Ramadan and the 1st week of post-Ramadan month (87.5% vs. 60.0%).

Discussion

In our study, the mean INR was significantly higher after Ramadan compared to the pre-Ramadan month (3.05 vs. 2.47, $p = 0.004$). INR was also insignificantly higher during Ramadan compared to pre-Ramadan (2.47 vs. 2.67, $p = 0.183$). Lai et al. [8] reported a statistically significant increase in INR in Ramadan compared to the months preceding and following months, which they attributed to dietary factors, changes in sleep patterns, and alterations in time of food and drug intake. By contrast, our study noticed a progressive increase in INR throughout the duration of the study. No difference in warfarin dose taken was found between the three study periods, which suggests that this increase in INR may be related to the factors suggested by Lai et al. [8]. In addition, it may be reasonable to consider differences of climate and seasonal foods as possible factors that may cause the difference between our results and those of Lai et al. [8].

Biochemical markers of hepatic dysfunction did not show any significant difference throughout the study period, which eliminates this factor as a possible reason behind the changes observed in INR levels. This is consistent with the data reported by Chamsi-Pasha et al. [6] who did not identify any evidence of liver dysfunction during Ramadan.

Due to the lack of evidence in this topic, some of our colleagues have hypothesized that fasting may lead to dehydration, and thus increase blood viscosity, which may predispose the patients to thrombotic events. In this study, we calculated the blood osmolarity after 9–11 hours of fasting using the equation:

$$2 \times (\text{Na} + \text{K}) + (\text{Glucose}/18) + (\text{BUN}/2.8). \qquad (2)$$

No significant difference in blood glucose and BUN levels was found. This contradicts the results of other metabolic studies which reported a decrease in glucose levels, high density lipoprotein, and body weight during Ramadan, along with an increase in low density lipoprotein [9,10]. This may be attributed to the fact that blood samples in these studies were obtained at least

12 hours after the last meal [9], whereas blood samples in our study were obtained earlier (about 9–11 hours after the last meal). By contrast, studies conducted by Rashed et al. [11] and Fedail et al. [12] reported a mild increase or a mild variation in blood glucose levels in Ramadan which supports the data presented in the current study. Mean sodium level was significantly higher during the pre-Ramadan month compared to Ramadan (139.67 mEq/L vs. 138.59 mEq/L; $p = 0.010$). Mean potassium level was significantly higher during Ramadan compared to the post-Ramadan month (4.53 mEq/L vs. 4.37 mEq/L; $p = 0.033$). Surprisingly, a significantly lower mean calculated blood osmolarity was found during the month of Ramadan compared to the pre- and post-Ramadan periods ($p < 0.05$). Therefore, we could not demonstrate any evidence of increased osmolarity that may lead to increased blood viscosity predisposing to thrombotic events. Moreover, no thrombotic (or hemorrhagic) events were documented throughout the study period.

In contrast to the results of Lai et al. [8], in our study, the best quality of anticoagulation was achieved during Ramadan, with 82.1% of the INR values obtained falling within the therapeutic range. Of the INR values obtained in the pre-Ramadan month, 23.3% were infratherapeutic; this ratio was noticed to decrease progressively over the study periods despite no significant change in the total amount of warfarin taken. A steep increase in the proportion of supratherapeutic INR values was noticed between Ramadan and the post-Ramadan months (4.5% and 18.9%; $p = 0.001$). This was reflected in a significant increase in the mean INR value between these months (from 2.67 to 3.05; $p = 0.004$). Again, these findings contradict those of Lai et al. [8], who reported a significant decrease in mean INR values between Ramadan and the post-Ramadan periods. In addition, Lai et al. [8] noticed a significant increase in time below therapeutic range in the post-Ramadan month. Therefore, we could not reproduce the results of the above mentioned study and we obtained a contradictory set of data.

The largest weekly fluctuation in the ratio of patients with optimal therapeutic anticoagulation was noticed between the last week of Ramadan and the 1st week of post-Ramadan period (87.5% vs. 60.0%). A similar observation was also noticed in Lai et al.'s study [8]. This difference is probably caused by the significant changes in dietary habits after Ramadan and the feast celebrated during the 1st week after Ramadan. Since the period of time within the therapeutic range significantly impact

clinical outcomes [13], it may be reasonable for clinicians to emphasize the importance of a close INR follow up during this period.

Limitations of this study include the low number of participants and enrolling patients in the follow-up program without ensuring that they had stable INR levels prior to enrolment. This might have affected the INR values especially in the first weeks of follow up. We intentionally chose to include all patients regardless of their previous anticoagulation profile so as to imitate the general population of patients taking warfarin for PHVs. Also, the study did not examine the INR levels of non-fasting patients. Comparison of the results of this study with this group of nonfasting patients might help to clarify further the effects of fasting on anticoagulation therapy. The small number of patients included decreases the power of this study and thus studies including larger numbers of patients need to be conducted to clarify further the effects of Ramadan fasting on the quality of anticoagulation with warfarin.

Conclusion

Although the best quality of anticoagulation was observed during Ramadan, a dramatic decrease in the therapeutic INR ratio occurred in the 1st week of the following month. Thus, clinicians should emphasize the importance of intensive INR follow up during this period.

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